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# Synthesis of 1-Amino-4-chloroisoquinoline. A New Approach to 1-Aminoisoquinoline

Antonio Nuvole and Gérard Aimé Pinna

Institute of Pharmaceutical Chemistry of the University, 07100 Sassari, Italy

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The as yet unknown 1-amino-4-chloroisoquinoline was synthesised from 1,4-dichloroisoquinoline through the 1-phenoxy-4-chloro derivative. This procedure was also suitable for obtaining 1-aminoisoquinoline from 1-chloroisoquinoline in good yields.

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During a pharmacological investigation of derivatives of 1-aminoisoquinoline (1), it became advisable to test compounds halogenated in the 3- and 4-positions of the heterocyclic nucleus.

To obtain these compounds, 1-amino-3-chloro- and 1-amino-4-chloroisoquinoline (2) were needed as intermediates. While the synthesis of the former was reported (1) to occur by aminolysis of 1,3-dichloroisoquinoline with aqueous ammonia at 175°, the isomer (2) was unexpectedly unknown.

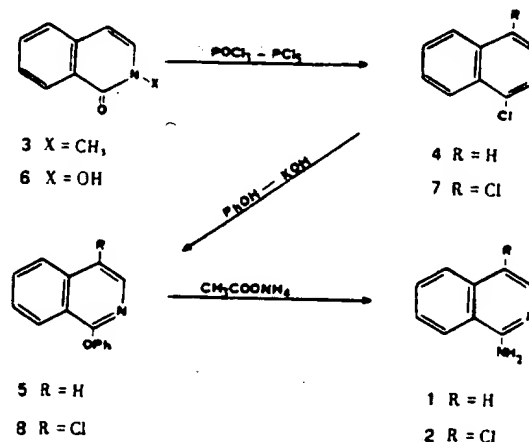
Attempts to obtain 2 by aminolysis from the known 1,4-dichloroisoquinoline (7) (2) led to recovery of the starting compound. We succeeded, however, in synthesising 2 from 7 in 46% overall yield by a procedure based on the replacement of the 1-chlorine atom with the more reactive phenoxy group. Accordingly, 7 was heated in phenol and potassium hydroxide at 120° for 15 hours to give 65% of 1-phenoxy-4-chloroisoquinoline (8), m.p. 58-59°, which was transformed into the desired 2 (70% yield), m.p. 134-135°, in molten ammonium acetate at 190°. The new compounds 8 and 2 were characterised by elemental analysis and nmr spectrum as reported in the experimental section.

In particular, the structures assigned to these compounds were supported by the nmr peak attributed to H-3, which appears as a sharp singlet at about  $\delta$  8, analogous with the H-3 signal of the starting material 7.

The pathway followed for 2 also constituted an alternate synthesis of 1 starting from 1-chloroisoquinoline (4) (3). This new approach which led to a 70% overall yield of 1 requires milder reaction conditions than those employed for 2 and offers the advantage of avoiding the direct amination of isoquinoline with potassium amide (4) or sodium amide (5), where a scale up could involve safety problems. Accordingly, 4 heated on steam bath with phenol and potassium hydroxide gave 80% of 1-phenoxyisoquinoline (5) (6), which was eventually transformed with ammonium acetate at 160° into compound 1 (87% yield).

It should be noted that the synthesis of the starting material 4, which was better accomplished from 2-methyl-1-isoquinolone (3) (7) is accompanied by the formation of about 15% of 7, which requires column chromatography to be removed. We have found, however, that for large-scale runs the time consuming purification of 4

## SCHEME



could be overcome, because of the poor reactivity of 7 under the reaction conditions which converted 4 into 5. Consequently, this step could be carried out with crude 4, with the unreacted 7 remaining in the mother liquor when crude 5 was crystallised. Overall yields of 4 → 1 were in this case slightly lower (63%).

Attempts to directly replace the 1-chlorine atom of 4 with an amino group were unsuccessful in spite of the smooth conversion of the related 4-chloroquinazoline (8) and 1-chlorophthalazine (9) into the corresponding amino derivatives.

## EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Ir spectra were taken with a Perkin Elmer model 297 spectrophotometer. Nmr were determined in deuteriochloroform with a 270 MHz Bruker spectrometer with TMS as internal reference.

### Synthesis of 1-Amino-4-chloroisoquinoline (2).

#### 1,4-Dichloroisoquinoline (7).

The procedure reported (2) in the literature involving heating 2-hydroxy-1-isoquinolone (6) (8.0 g., 0.05 mole) with excess phosphorus oxychloride (80 mL) at 160° in a sealed tube for 3 hours gave 4.75 g. (48%) of 7, m.p. 92-94° (lit. (2) 44%, m.p. 90-92°); nmr:  $\delta$  7.73 and 7.85 (m, H-6 and H-7), 8.17 (d, J = 8 Hz, H-5), 8.20 (d, J = 8 Hz, H-8), 8.23 (s, H-3).

## 1-Phenoxy-4-chloroisoquinoline (8).

A mixture of **7** (10 g., 0.051 mole), phenol (47 g., 0.5 mole) and powdered potassium hydroxide (5.6 g., 0.10 mole) was heated at 120° for 15 hours.

The unreacted phenol was basified with an excess of 20% sodium hydroxide and the resulting milky suspension was extracted with benzene. The organic layer was washed with 5% sodium hydroxide, then with water. After drying over sodium sulphate, the solvent was evaporated and the solid residue (12.5 g.) was crystallised from 12 ml. of ethanol to give 8.4 g. (65%) of **8**, m.p. 58-59°, nmr:  $\delta$  7.24-7.36 (m, 5H, OPh), 7.70 and 7.85 (m, H-6 and H-7), 8.01 (s, H-3), 8.15 (d, J = 8 Hz, H-5), 8.46 (d, J = 8 Hz, H-8).

Anal. Calcd. for  $C_{15}H_{10}ClNO$ : C, 70.46; H, 3.94; N, 5.48; Cl, 13.86. Found: C, 70.29; H, 3.99; N, 5.52; Cl, 13.93.

## 1-Amino-4-chloroisoquinoline (2).

An intimate mixture of **8** (12 g., 0.047 mole) and ammonium acetate (45 g., 0.58 mole) was heated at 190° for 15 hours. The molten mass was cooled and dissolved into 150 ml. of water. Unreacted **8** (2.3 g.) was removed by filtration and the aqueous layer was made alkaline with solid sodium hydroxide.

The precipitate was extracted with ether; the organic layer was dried over sodium sulphate and evaporated to give 4.85 g. (71.6% on the reacted **8**) of **2**, m.p. 134-135° (benzene); nmr:  $\delta$  5.37 (broad s, 2H,  $NH_2$ ), 7.55 and 7.74 (m, H-6 and H-7), 7.79 (d, J = 8 Hz, H-5), 8.00 (s, H-3), 8.09 (d, J = 8 Hz, H-8).

Anal. Calcd. for  $C_9H_7ClN_2$ : C, 60.51; H, 3.95; N, 15.69; Cl, 19.85. Found: C, 60.76; H, 3.98; N, 15.49; Cl, 19.72.

## Synthesis of 1-Aminoisoquinoline (1).

## 1-Chloroisoquinoline (4).

The method reported in the literature (3) was modified as follows: **3** (20 g.), phosphorus pentachloride (30 g.) and phosphorus oxychloride (30 ml.) were heated in a sealed tube at 150° for 24 hours.

After cooling, the excess of phosphorus oxychloride was distilled off at reduced pressure and the oily residue was poured into ice. The aqueous mixture was made alkaline with 20% sodium hydroxide and was extracted with ether. The organic layer was dried over sodium sulphate and the solvent was evaporated. The oily residue (A) (20 g.) was chromatographed on silica gel column eluting with benzene and collecting in the order **4** g. (16%) of **7**, m.p. 89.91° and 14.1 g. (68.6%) of **4**, m.p. 34-36° (lit. (3) b.p. 143-145°/15 mm); nmr:  $\delta$  7.56 (d, J = 6 Hz, H-4), 7.63 and 7.64 (m, H-6 and H-7), 7.80 (d, J = 8 Hz, H-5), 8.25 (d, J = 6 Hz, H-3), 8.28 (d, J = 8 Hz, H-8).

## 1-Phenoxyisoquinoline (5).

## a) From Pure 4.

A mixture of **4** (4.9 g., 0.03 mole), potassium hydroxide (3.4 g., 0.06 mole) and phenol (28.2 g., 0.3 mole) was heated on a steam-bath for 6 hours and worked up as reported for **8**. The solid residue crystallised from ethanol to give 5.3 g. (80%) of **5**, m.p. 68-69° (lit. (6) 69°).

## b) From Crude 4.

The oily product (A) (108 g., 76 g. pure **4**) was allowed to react with potassium hydroxide (1.7 g.) and phenol (140 g.) as indicated above. The solid residue (103 g.) was triturated with ethanol (150 ml.) and filtered, to give 52.5 g. of **5**, m.p. 66-67°. The filtrate after concentration and cooling separated a solid product (42 g.), m.p. 43-48° which was further crystallised from five volumes of ethanol to give an additional 22 g. of **5**, m.p. 65-67°; total yields 74.5 g. (72.5% on pure **4**). The alcoholic filtrates were evaporated to give a semi-solid residue which was chromatographed on silica gel column eluting with benzene and collecting in the order 5.5 g. of **8**, 16 g. of **7** and 4.2 g. of **5**.

## 1-Aminoisoquinoline (1).

A mixture of **5** (60 g., 0.271 mole) and ammonium acetate (154 g., 2 moles) was heated at 160° for 4 hours and worked up as reported for **2** to give 34 g. (87%) of **1**, m.p. 120-121° (benzene) (lit. (4) 122-123°).

Attempts to obtain **1** by heating **4** at 100° for 5 hours in saturated ethanolic ammonia, or by allowing **4** to react with concentrated aqueous ammonia at room temperature for 10 days led to the recovery of unreacted material.

## Acknowledgment.

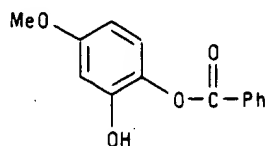
We wish to thank Professor G. Cignarella for his counsel and Professor G. G. Gallo (Lepetit, Milan) for the nmr spectra.

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TI 3-(Hydroxy or hydroxymethyl)-4-hydroxy-alpha(aminomethyl)benzyl alcohols and methods of use

IN Minatoya, Hiroaki, East Greenbush, NY, United States  
Tullar, Benjamin F., Laurel Park, NC, United States  
Conway, Walter D., Amherst, NY, United States

PA Sterling Drug Inc., New York, NY, United States (U.S. corporation)

PI US4336400 820622

AI 78US-0937949 780830 (5)

RLI Division of Ser. No. 76US-0654700, filed on 2 Feb 1976, now patented, Pat. No. US4138581 which is a continuation-in-part of Ser. No. 74US-0496538, filed on 12 Aug 1974, now Defensive Publication No. which is a division of Ser. No. 71US-0123834, filed on 12 Mar 1971, now patented, Pat. No. US3904671 which is a continuation-in-part of Ser. No. 69US-0812370, filed on 1 Apr 1969, now abandoned

DT Utility

EXNAM Primary Examiner: Killos, Paul J.

LREP Dupont, Paul E.; Wyatt, B. Woodrow

CLMN Number of Claims: 81

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3976

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mono-, di- and tri-esters of 3-(hydroxy or hydroxymethyl)-4-hydroxy-alpha-(aminomethyl)benzyl alcohols, obtained by methods involving reduction of the corresponding mono- and di-ester ketones, are useful for producing sympathomimetic effects, such as bronchodilation, of long duration with low cardiovascular stimulating effect, in warm-blooded mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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